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February 23, 2004

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

RE: ANDA Suitability Petition
Esmolol Hydrochloride for Injection

ANDA Suitability Petition

The undersigned submits this Suitability Petition (the "Petition") under the provisions of the Federal Food, Drug and Cosmetic Act, Section, 505(j)(2)(C) and 21 CFR 314.93 to request the Commissioner of Food and Drugs to allow the Petitioner to file an Abbreviated New Drug Application (ANDA) for Esmolol Hydrochloride for Injection, 2500 mg/vial in a lyophilized dosage form.

A. Action Required

This petition seeks a determination that the proposed Esmolol Hydrochloride for Injection, 2,500 mg/vial in a lyophilized form is suitable for evaluation under an ANDA. This Petition further requests an ommission from the requirement to provide a pediatric assessment as described in the current regulations for a new dosage form.[1]

B. Statement of Grounds

The subject of the Petition for Esmolol Hydrochloride for Injection is to permit a change in the dosage form (powder vs. solution) based on the following reasons.

1. The stability of the product is enhanced in the lyophilized form versus the aqueous form. During pilot studies, a lower impurity profile has been observed in the lyophilized form than what has been observed in the reference listed drug (At the expiry, total impurities in Brevibloc® Injection – 5.7%, where for Esmolol HCl for Injection – 0.16%).

1. The Pediatric Research Equity Act of 2003, Section 2; CFR314.55; Best Pharmaceuticals for Children Act of 2002; and Section 505(j)(2)(C)(i) of the Federal FD&C Act

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2. The new dosage form may help to prevent fatal medication errors. The Reference Listed Drug has two different concentrations, a 10 mg/mL and a 250 mg/mL, which are both 10 mL volumes and are both clear colorless solutions. The 10 mg/mL is a "ready to use" solution, while the 250mg/mL concentrate must be diluted prior to use. There have been multiple reports of medication errors when the concentrate is directly administered without dilution instead of administering the "ready to use" solution.[2] Many of these medication errors have proven to be fatal. The new lyophilized dosage may not prevent all of these errors, but should provide some advantage over two liquid dosages which have very similar appearances. The lyophilized formulation would first have to be reconstituted prior to use in addition to the required IV dilution. This additional step should alert the pharmacist that it is not the ready to use solution as it would not be the normal pattern for the pharmacist or nurse on the floor. With the current Brevibloc products, the nurse on the floor can open the product and administer the product directly as a bolus, often confusing the two products and causing a potentially fatal occurrence.

3. The new dosage form allows the availability of a cheaper equivalent form of the drug product to the patient population, in a timely manner that does not infringe the rights of the innovator.

The proposed product is equivalent in use, dosage, and route of administration to the listed drug Brevibloc® Injection, and the concentration of the proposed product is in accordance with the FDA approved labeling for Brevibloc® Injection (Attachment II). For these reasons, the proposed drug product is expected to have the same therapeutic effect as the reference listed drug when administered to patients. The proposed drug product will be packaged in a concentrate form same as reference listed drug, but in a different dosage form. The formulation of Brevibloc® Injection and the proposed Esmolol Hydrochloride for Injection are presented in Table 1.

Table 1. Comparison of the Reference Listed Drug and the Proposed Drug Product

Product	Dosage Form	Route of Administration	Total Drug Concentration	Ingredient
Brevibloc® Injection	Sterile Solution	Intravenous	2,500 mg/vial	Esmolol HCl
Proposed Drug Product	Sterile Powder	Intravenous	2,500 mg/vial	Esmolol HCl

The proposed drug product will be reconstituted using 23 mL of water for injection for a reconstituted concentration of 100 mg/mL. Furthermore it is diluted to 10 mg/mL of final concentration using the listed intravenous fluids from the package insert labeling. The subject drug product is intended for use only as described in the Dosage and Administration section of the package insert provided in Attachment I.

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2. ISMP Medication Safety Alerts, Dated January 18, 1998 and May 21, 1997.See Attachment III.

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Pediatric Exclusivity has been granted to Brevibloc® Injection, extending the patent life from June 3, 2003 to December 3, 2003. The Pediatric Research Equity Act of 2003 (Section 2, (b)(3)(ii)(I)) states that "No assessment may be required under paragraph (1) for a drug subject to an approved application under section 505 unless....(ii)(I) the request was made under section 505A(c)- (aa) the recipient of the written request does not agree to the request" A written request was issued to Baxter Healthcare. Baxter agreed to the written request and performed the requested pediatric studies, thus gaining six months of exclusivity. Therefore, it is our contention that a pediatric assessment is not necessary to support this petition as the studies have already been conducted by Baxter Healthcare on the active compound, Esmolol.

For the above listed reasons, it is believed that the proposed Esmolol Hydrochloride for Injection, 2500 mg per vial is suitable for evaluation under an ANDA.

C. Environment Impact

Action on an ANDA is categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR 25.31 (a).

D. Economic Impact

Not Applicable

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the Petition.

Sincerely,
for Bedford Laboratories™

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Esmolol HCl for Injection Concentrate

ANDA Suitability Petition

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